SYNTHESIS AND SOME REACTIONS OF 1-PHENYLIMIDAZO[5,1-b] BENZOXAZOLE

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The condensation of o-aminophenol with ethyl hippurate has given 2-benzoylaminomethylbenzoxazole (I) and N-hippuroyl-o-aminophenol (II). The cyclization of both I and II in the presence of phosphorus oxychloride in benzene or toluene leads to the formation of 1-phenylimidazo[5,1-b]benzoxazole (III). Compound III has been brominated in position 3 and has been subjected to the Mannich and Vilsmeier reactions. A number of derivatives of III containing various substituents in position 3 has been obtained.

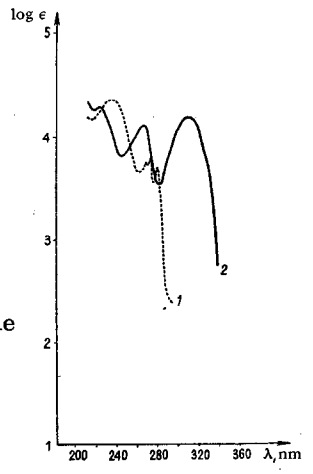
In one of the preceding communications [1], we described the synthesis of 3-phenylimidazo[5,1-b]benzoxazole, a representative of a new heterocyclic system.

In this paper we describe the synthesis of imidazo[5,1-b]benzoxazole containing a phenyl residue in position 1 and the preparation of some of its 3-substituted derivatives. The starting material for the synthesis of the 1-phenylimidazo [5,1-b]benzoxazole (III) was o-aminophenol, which was subjected to condensation with ethyl hippurate. From the highly-resinified reaction mixture, three compounds were isolated. One of them, insoluble in dilute alkalis, consisted of 2-benzoylaminomethylbenzoxazole (I); and the second, soluble in alkali, proved to be an intermediate substance—N-hippuroyl-o-aminophenol (II). When the reaction was carried out at 165–170° C, compound II was formed in a predominating amount; at a higher reaction temperature (~200° C) it cannot be isolated. In the ethereal solution remaining after the original treatment of the reaction mixture 2-phenbenzoxazole was detected.

Attempts to carry out the condensation of o-aminophenol with the ethyl ester of N-acetylglycine in order to obtain 2-acetylaminomethylbenzoxazole did not lead to the desired result: pronounced resinification took place and it was impossible to isolate an individual substance.

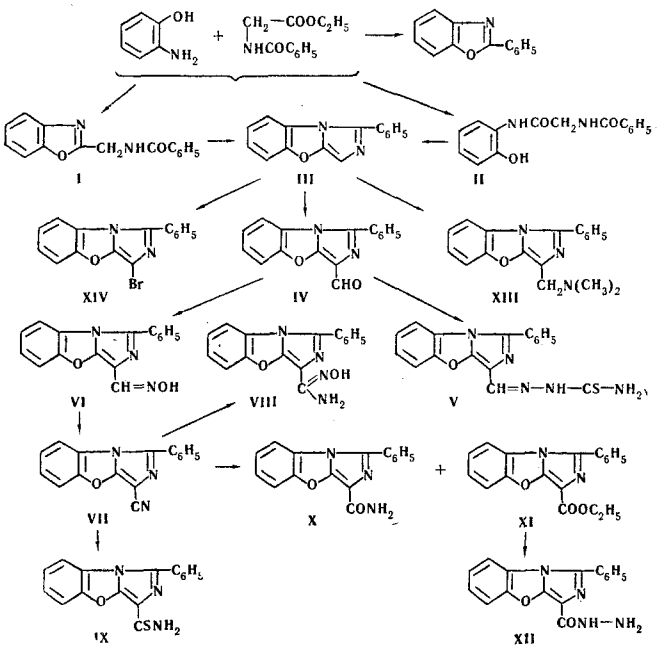
When I was subjected to prolonged heating in benzene or toluene in the presence of phosphorus oxychloride, the closure of the third ring and the formation of III took place. The latter was also obtained by heating II with phosphorus oxychloride.

The UV spectrum of III differs markedly from the spectrum of I (figure) and shows a considerable bathochromic shift as compared with the UV spectrum of 3-phenylimidazo[5,1-b]benzoxazole [1].



UV spectra (in ethanol): 1) 2-benzoylaminomethylbenzoxazole (I); 2) 1-phenylimidzao[5,1-b]benzoxazole (III).

As we have shown [2], 3-phenylimidazo[5,1-b]benzoxazole is capable of taking part in some electrophilic substitution reactions at position 1. It could be expected for compound III that substitution would take place readily in position 3, since the carbon atom in this position also has an increased π-electron density [3].



The Vilsmeier reaction was carried out under the same conditions as in the case of 3-phenylimidazo[5, 1-b]benzoxazole [2], giving a high yield of 1-phenylimidazo[5, 1-b]benzoxazole-3-aldehyde (IV). From this, the thiosemicarbazone (V) and the oxime (VI) were obtained. Under the action of acetic anhydride in the presence of sodium acetate, the oxime (VI) was converted into 1-phenylimidazo[5, 1-b]benzoxazole-3-carbonitrile (VII) with a yield considerably greater than for 3-phenylimidazo-[5, 1-b]benzoxazole-1-carbonitrile, obtained by an analogous method [2].

When an attempt was made to obtain an ester from VII (via the imidic ester), a mixture of approximately equal amounts of the amide (X) and the ester (XI) was isolated. When XI was heated with an excess of hydrazine hydrate in ethanol, a low yield of 1-phenylimidazo[5, 1-b]benzoxazole-3-carbohydrazide (XII) was obtained. The amide oxime (VIII) and the thioamide (IX) were obtained from the nitrile (VII); it was found that the thioamide did not form under the usual conditions (at 20–25° C); the reaction took place only at 70° C, with a moderate yield. The action on III of a paraformaldehyde and dimethylamine hydrochloride in isoamyl alcohol gave the Mannich base XIII in which the position of the dimethylaminomethyl group was confirmed by the PMR spectrum. With methyl iodide, XIII readily formed monomethiodide.

In view of the fact that the bromination of 3-phenylimidazo[5, 1-b]benzoxazole takes place with a better yield when bromosuccinimide is used [2], we employed the same method for the introduction of bromine into III, and obtained 3-bromo-1-phenylimidazo[5, 1-b]benzoxazole (XIV). When an attempt was made to acetylate III by heating it with acetic anhydride in acetic acid, the starting material was recovered unchanged.

On comparing the reactivity of III and 3-phenylimidazo[5, 1-b]benzoxazole, it may be concluded that electrophilic substitution reactions and also some reactions of the radical type (bromination with bromosuccinimide) take place equally readily in the two compounds, judging from the yields of derivative formed and conditions for their preparation.

In a study of III and its derivatives for their antibacterial activity (carried out in the chemotherapy division of VNIKhFI [Ordzhonikidze All-Union Chemical and Pharmaceutical Scientific-Research Institute] by S. N. Milovanova and T. N. Zykova), no compounds possessing appreciable bacteriostatic activity were found.

EXPERIMENTAL

Reaction of o-aminophenyl with ethyl hippurate. A well-ground mixture of 2.02 g (18.5 mM) of o-aminophenol and 3.83 g (18.5 mM) of ethyl hippurate [4] was heated with the passage of nitrogen at 185–187° C and then for another 2 hr at 200° C. After cooling, the dark viscous mass was triturated with a small amount of ether and the precipitate that formed was washed with 5% caustic soda and then with water. This gave 1.45 g (31%) of

2-benzoylaminomethylbenzoxazole (I) with mp 129–133° C. After recrystallization from 50% methanol, mp 136–137° C. Faintly yellow crystals readily soluble in ethanol and acetone, moderately soluble in ether, and insoluble in water, petroleum ether, and dilute acids and alkalis were obtained. Found, %: C 71.7; H 4.7; N 11.2. $C_{15}H_{12}N_2O_2$. Calculated %: C 71.4; H 4.8; N 11.1. The alkaline solution from the washing of the technical I was acidified with acetic acid, and the precipitate was filtered off and washed with water. This gave 0.14 g of N-hippuroyl-o-aminophenol (II), mp 208–209° C (from aqueous ethanol). Found, %: C 66.7; H 5.4; N 10.4. $C_{15}H_{14}N_2O_3$. Calculated, %: C 66.7; H 5.2; N 10.4. The ethereal solutions remaining after the trituration of the reaction mixture were washed with 5% caustic soda solution, and and then the ether was evaporated off and the residue was crystallized from methanol with the addition of charcoal. This gave 0.1 g of 2-phenylbenzoxazole, mp 103–104° C, identical with an authentic sample [5].

1-Phenylimidazo[5,1-b]benzoxazole (III). A suspension of 1.82 g (7.2 mM) of I in 24.2 ml of dry benzene and 5.6 ml of redistilled phosphorus oxychloride was boiled for 42 hr 30 min, by which time the evolution of hydrogen chloride had ceased. The benzene layer was decanted off and the residual dark vitreous mass was triturated with ice, dry sodium carbonate was added until the reaction was alkaline, and the resulting precipitate was filtered off and carefully washed with water. Weight 1.24 g (73%), mp 96.5–98° C (from aqueous methanol). Almost colorless crystals in the form of plates readily soluble in ethanol and 10% hydrochloric acid, insoluble in dilute alkalis were obtained. Found, %: C 77.3; H 4.3; N 12.1. $C_{15}H_{10}N_2O$. Calculated, %: C 76.9; H 4.3; N 12.0. When II was heated with phosphorus oxychloride under the same conditions, a compound identical with III was obtained (yield ~30%). **Picrate of III**, mp 228–229° C (from ethanol). Found, %: C 54.6; H 2.8; N 15.3. $C_{15}H_{10}N_2O \cdot C_6H_3N_3O_7$. Calculated, %: C 54.4; H 2.8; N 15.1. **The hydrochloride of III** was obtained by treating III with an ethanolic solution of hydrogen chloride. Colorless crystals with mp 253–256° C (from ethanol). Found, %: C 66.5; H 4.0; N 10.2; Cl 13.2. $C_{15}H_{10}N_2O \cdot HCl$. Calculated, %: 66.5; H 4.1; N 10.4; Cl 13.1.

1-Phenylimidazo[5,1-b]benzoxazole-3-aldehyde (IV). To 3.5 ml of purified dimethylformamide at 0–5° C was gradually added 0.5 ml (5.5 mM) of redistilled phosphorus oxychloride, the mixture was stirred at 20° C for 10–15 min, a solution of 0.5 g (2.14 mM) of III in 4.5 ml of dimethylformamide was added, and the mixture was heated at 100° C for 2 hr, cooled, and poured onto ice. The precipitate was filtered off, triturated with a saturated aqueous solution of sodium acetate, filtered off, and washed with water. This gave 0.5 g (89%) of IV. Colorless crystals with mp 174–176° C (from ethanol). Found, %: C 72.8; H 3.9; N 10.4. $C_{16}H_{10}N_2O_2$. Calculated, %: C 73.3; H 3.8; N 10.7

Thiosemicarbazone of IV (V), mp 228–230° C (from ethanol). Yield 99.5%. Found, %: C 60.8; H 4.1; S 9.2. $C_{17}H_{13}N_5OS$. Calculated, %: C 60.9; H 3.9; S 9.5.

Oxime of IV (VI). Colorless crystals with mp 210–211° C (from butanol). Yield 91%. Found, %: C 69.3; H 4.1; N 15.1. Calculated for $C_{16}H_{11}N_3O$, %: C 69.3; H 4.0; N 15.1.

1-Phenylimidazo[5,1-b]benzoxazole-3-carbonitrile (VII). Colorless crystals with mp 183–185° C (from ethanol). Yield 99.2%. Found, %: C 74.1; H 3.6; N 16.3. $C_{16}H_9N_3O$. Calculated, %: C 74.1; H 3.5; N 16.2.

1-Phenylimidazo[5,1-b]benzoxazole-3-carboxamide oxime (VIII). Colorless crystals with decomp. p. 217–218° C (from pyridine). Found, %: C 66.1; H 4.3. $C_{16}H_{12}N_4O_2$. Calculated, %: C 65.7; H 4.1.

1-Phenylimidazo[5,1-b]benzoxazole-3-carbothioamide (IX). A suspension of 0.5 g (1.94 mM) of VII in 15 ml of absolute ethanol was treated with 0.8 ml of triethylamine, and a current of dry hydrogen sulfide was passed into the mixture at 70° C for 3 hr. After cooling, the precipitate was filtered off, giving 0.34 g of IX in the form of a colorless crystalline substance with mp 226–227° C (from glacial acetic acid). Found, %: C 65.8; H 3.7; S 10.5. $C_{16}H_{11}N_3OS$. Calculated, %: C 65.5; H 3.8; S 10.9.

1-Phenylimidazo[5,1-b]benzoxazole-3-carboxamide (X). A current of dry hydrogen chloride was passed into a boiling solution of 1 g (3.87 mM) of VII in 65 ml of absolute ethanol for 3 hr 30 min, and then the mixture was evaporated to 1/3 of its original volume and cooled, and the precipitate was filtered off, washed with absolute ethanol, and treated with 5% aqueous sodium bicarbonate. This gave 0.34 g of X, mp 250° C (from ethanol). Found, %: C 69.2; H 3.7; N 14.9. $C_{16}H_{11}N_3O_2$. Calculated, %: C 69.3; H 4.0; N 15.1.

Ethyl 1-phenylimidazo[5,1-b]benzoxazole-3-carboxylate (XI). The acid ethanolic mother liquor from **X** (see preceding experiment) was treated with a double volume of water and neutralized with saturated sodium acetate solution. The precipitate formed was filtered off and washed with water, giving 0.64 g of XI, mp 204.5–206.5° C (from methanol). Found, %: C 70.9; H 4.8; N 9.0. $C_{18}H_{14}N_2O_3$. Calculated, %: C 70.6; H 4.6; N 9.1.

1-Phenylimidazo[5,1-b]benzoxazole-3-carbohydrazide (XII). A suspension of 0.5 g (1.65 mM) of XI in a mixture of 2.5 ml of absolute ethanol and 2.5 ml (50 mM) of hydrazine hydrate was heated at 125–130° C (bath temperature) for 30 min, and was then cooled and the precipitate was filtered off. This gave 0.15 g of XII. Colorless crystals in the form of needles readily soluble in chloroform and hot ethanol were obtained; mp 216.5–218° C (from methanol). Found, %: C 65.6; H.4.0; N 18.9. $C_{16}H_{12}N_4O_2$. Calculated, %: C 65.7; H 4.2; N 19.2. The mother liquor yielded 0.19 g of a substance of unknown structure with decomp. p. 195° C (from ethanol), insoluble in chloroform.

3-Bromo-1-phenylimidazo[5,1-b]benzoxazole (XIV). A solution of 1.04 g (4.45 mM) of III and 0.79 g (4.45 mM) of bromosuccinimide in 26 ml of carbon tetrachloride was boiled for 1 hr 30 min, the succinimide was filtered off, and the filtrate was evaporated to dryness. The residue was crystallized from ethanol, giving 0.98 g of XIV, mp 154–156° C (from ethanol). Found, %: C 57.5; H 2.8; N 9.0; Br 25.4. $C_{15}H_9BrN_2O$. Calculated, %: C 57.5; H 2.9; N 9.0; Br 25.5.

3-Dimethylaminomethyl-1-phenylimidazo[5,1-b]benzoxazole (XIII). A mixture of 1 g (4.27 mM) of III, 0.26 g (8.68 mM) of paraformaldehyde, 0.45 g (5.53 mM) of dimethylamine hydrochloride, and 12 ml of isoamyl alcohol was boiled for 5 hr and cooled, and the precipitate was filtered off, treated with ~10 ml of water, and filtered off again, and the solution was saturated with gaseous ammonia. This gave 0.77 g (62%) of III with mp 85–86° C (from hexane). Found, %: C 74.2; H 5.8; N 14.1. $C_{18}H_{17}N_3O$. Calculated, %: C 74.2; H 5.9; N 14.4.

Methiodide of XIII, mp 218–223 ° C (from ethanol). Yield 96%. Found, %: C 52.5; H 4.6; N 9.2; I 29.3; $C_{19}H_{20}IN_3O$. Calculated, %: C 52.7; H 4.6; N 9.7; I 29.3.

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